ORIGINAL ARTICLE

Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation

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ABSTRACT

BACKGROUND

Bronchoscopic lung-volume reduction with the use of one-way endobronchial valves is a potential treatment for patients with severe emphysema. To date, the benefits have been modest but have been hypothesized to be much larger in patients without interlobar collateral ventilation than in those with collateral ventilation.

METHODS

We randomly assigned patients with severe emphysema and a confirmed absence of collateral ventilation to bronchoscopic endobronchial-valve treatment (EBV group) or to continued standard medical care (control group). Primary outcomes were changes from baseline to 6 months in forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and 6-minute walk distance.

RESULTS

Eighty-four patients were recruited, of whom 16 were excluded because they had collateral ventilation (13 patients) or because lobar segments were inaccessible to the endobronchial valves (3 patients). The remaining 68 patients (mean [±SD] age, 59±9 years; 46 were women) were randomly assigned to the EBV group (34 patients) or the control group (34). At baseline, the FEV_1 and FVC were 29±7% and 77±18% of the predicted values, respectively, and the 6-minute walk distance was 374±86 m. Intention-to-treat analyses showed significantly greater improvements in the EBV group than in the control group from baseline to 6 months: the increase in FEV_1 was greater in the EBV group than in the control group by 140 ml (95% confidence interval [CI], 55 to 225), the increase in FVC was greater by 347 ml (95% CI, 107 to 588), and the increase in the 6-minute walk distance was greater by 74 m (95% CI, 47 to 100) (P<0.01 for all comparisons). By 6 months, 23 serious adverse events had been reported in the EBV group, as compared with 5 in the control group (P<0.001). One patient in the EBV group died. Serious treatment-related adverse events in this group included pneumothorax (18% of patients) and events requiring valve replacement (12%) or removal (15%).

CONCLUSIONS

Endobronchial-valve treatment significantly improved pulmonary function and exercise capacity in patients with severe emphysema characterized by an absence of interlobar collateral ventilation. (Funded by the Netherlands Organization for Health Research and Development and the University Medical Center Groningen; Netherlands Trial Register number, NTR2876.)

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Bronchoscopic lung-volume reduction with the use of one-way endobronchial valves has emerged as a potential treatment for patients with severe emphysema. This treatment was previously investigated in the randomized, controlled Endobronchial Valve for Emphysema Palliation Trial (VENT),[1] which showed significant but moderate improvements in forced expiratory volume in 1 second (FEV_1): an increase from baseline of 4.3% (95% confidence interval [CI], 1.4 to 7.2). Post hoc analyses of the VENT data suggested that endobronchial-valve treatment might be more effective in patients who had a complete fissure (as compared with an incomplete fissure) between the lobe that was targeted for treatment and the adjacent lobe on high-resolution computed tomography (HRCT) and when endobronchial-valve treatment resulted in complete occlusion of the target lobe.[1]

A complete fissure on HRCT is a surrogate finding for the absence of interlobar collateral ventilation; if there is collateral ventilation, an occluded lobe can be reinflated through its collaterals.[2] It is difficult to assess the completeness of the fissure on HRCT in order to predict the absence of collateral ventilation, with considerable interobserver variation.[3] Temporary bronchoscopic lobar occlusion, achieved by inflation of a balloon catheter in the lobar bronchus, is another way to assess collateral ventilation. When combined with HRCT, this method has been shown to increase the predictability of lung-volume reduction after endobronchial-valve treatment.[4] We conducted a randomized, controlled study, called STELVIO, to examine the effectiveness of endobronchial-valve treatment in patients with severe emphysema in whom the absence of collateral ventilation had been proved.

Methods

Study Design and Oversight

This was a randomized, controlled study comparing endobronchial-valve treatment with standard medical care,[5] with crossover at 6 months to endobronchial-valve treatment for patients assigned to standard medical care. The study was performed, in accordance with the provisions of the Declaration of Helsinki, at the University Medical Center Groningen (UMCG), in the Netherlands, and was approved by the UMCG ethics committee. All patients gave written informed consent. All devices were obtained commercially from Pulmonx (all catheters at regular market prices and all valves at 50% of the market list price); Pulmonx was not involved in any part of the study.

Patients

Patients with emphysema who were older than 35 years of age and had stopped smoking more than 6 months earlier were eligible for the study if they had a post-bronchodilator FEV_1 that was less than 60% of the predicted value, total lung capacity (TLC) that was more than 100% of the predicted value, and residual volume that was more than 150% of the predicted value, with a score on the Modified Medical Research Council (mMRC) scale[6] of more than 1 (on a scale of 0 to 4, with higher scores indicating more severe dyspnea). An additional criterion for eligibility was a lobe that was determined to be a target for treatment, with a complete or nearly complete fissure between the target lobe and the adjacent lobe as visually judged on HRCT. The main exclusion criteria were evidence of collateral ventilation in the target lobe and failure to achieve lobar occlusion with endobronchial valves, as noted below.

Randomization

We randomly assigned patients in a 1:1 ratio to receive endobronchial-valve treatment (EBV group) or standard care (control group), using a randomization list that was computer-generated in blocks of four. The principal investigator and study personnel did not have access to the list. The generated codes were placed in opaque sealed envelopes, which were numbered sequentially. After completion of baseline measurements (pulmonary-function tests, 6-minute walk distance, and questionnaires) and when study criteria apart from bronchoscopy had been met, the assigned envelope was opened before bronchoscopy in the presence of the patient and bronchoscopist. Bronchoscopy was then performed, and patients with collateral ventilation or airways unsuitable for endobronchial-valve placement were excluded. When a patient was excluded, the treatment assignment was placed in a newly sealed envelope and inserted back into the randomization sequence.

PROCEDURES

Collateral ventilation was assessed by means of the Chartis system (Pulmonx) as previously described.[4] Briefly, during bronchoscopy (performed with a flexible bronchoscope [Olympus BF-1TQ180] with a 2.8-mm working channel) while the patient was under conscious sedation (with the administration of propofol and remifentanil), the target lobar airway was temporarily occluded by means of a balloon catheter, which blocks inspiratory flow but allows expiratory flow. A continuous expiratory flow through the catheter indicates collateral ventilation, and a flow gradually declining to zero indicates no collateral ventilation. Zephyr endobronchial valves (Pulmonx) were placed in all segments or subsegments of the target lobe as previously described, with the patient under either general anesthesia or conscious sedation.[1,4] Valve placement was performed during the initial bronchoscopic procedure for patients assigned to the EBV group and at 6 months for patients assigned to the control group.

OUTCOME MEASURES

Primary outcome measures were improvements from baseline to 6 months in FEV_1, forced vital capacity (FVC), and 6-minute walk distance in the EBV group as compared with the control group. Secondary outcome measures, among patients who completed the study, were improvements from baseline to 6 months in FEV_1, forced vital capacity (FVC), 6-minute walk distance, the total score on the St. George's Respiratory Questionnaire (SGRQ; scores range from 0 to 100, with higher scores indicating worse quality of life),[7,8] the score on the Clinical COPD (chronic obstructive pulmonary disease) Questionnaire (CCQ; scores range from 0 to 6, with higher scores indicating worse functioning),[9] and the total volume of the treated lobe on inspiratory HRCT. Clinical response was defined on the basis of established minimal clinically important differences from baseline (FEV_1, a 10% increase[10]; 6-minute walk distance, a 26-m increase[11]; SGRQ score, a 4-point reduction[8]; CCQ score, a 0.4-point reduction[9]; total volume of the treated lobe, a 350-ml reduction[2]; and residual volume, a 430-ml reduction[12]). Safety data were collected during the study. At baseline and at 1 month and 6 months of follow-up, the 6-minute walk test was performed according to American Thoracic Society recommendations,[13] and the SGRQ,[7] CCQ,[9] and mMRC[6] scores were obtained. Spirometry, whole-body plethysmography, and carbon monoxide diffusing capacity (measured with the Jaeger MasterScreen, CareFusion) were performed according to American Thoracic Society–European Respiratory Society guidelines[14,15] by assessors who were unaware of the study-group assignments. HRCT was performed at baseline and at 6 months after endobronchial-valve treatment. Target-lobe selection and fissure integrity were assessed visually on the baseline inspiratory HRCT scan (SOMATOM Sensation 64 eco, Siemens Healthcare; slice thickness, 1.0 mm) with the use of the AquariusNET viewer V4.4.7.85 (TeraRecon). After study completion, computerized quantifications were performed on the HRCT data set (Thirona Lung Quantification, version 15.01 [Thirona]).[16,17] We calculated lobar volumes and the percentage of voxels of less than −950 Hounsfield units (an indicator of the fraction of emphysematous lung). We classified the distribution of emphysema in the treated lung as homogeneous if the destruction scores for the upper and lower lobes differed by less than 15% and as heterogeneous if the scores differed by 15% or more.

STATISTICAL ANALYSIS

The initial sample size was based on the available post hoc analyses of the active treatment groups in the VENT, international VENT, and Chartis trial[1,2,4] and on our preliminary findings. With an alpha level at 5% and a beta level at 20%, we calculated that we would need to randomly assign 28 patients to the study groups (14 per group), all of whom could be fully evaluated with respect to the change in the percentage of the predicted FEV_1. A subsequent interim analysis for safety, withdrawal from the study, and assessment of the accuracy of FEV_1 assumptions showed a higher pneumothorax rate and a lower mean difference from baseline for the percentage of the predicted FEV_1 than we had assumed. To account for these findings, 68 patients were deemed necessary for randomization. A two-sample t-test and Fisher's exact test were performed to test for differences between groups at baseline. Intention-to-treat analyses were performed on the primary end points; if there were no available data after study exit, then multiple imputation was used for missing

data. Primary, secondary, and other efficacy outcomes were also evaluated in analyses restricted to patients who completed the study. Paired t-tests were used, or in the absence of a normal distribution, the Wilcoxon signed-rank test was used, to compare the groups with respect to changes from baseline to 6 months in study outcomes. Bonferroni correction was performed for multiple comparisons for the three primary end points. P values of less than 0.0167, for primary

Table 1. Baseline Characteristics of the Patients.*

Characteristic	EBV Group (N=34)	Control Group (N=34)
Female sex — no. (%)	18 (53)	28 (82)
Age — yr	58±10	59±8
Body-mass index†	24.1±3.5	24.2±4.0
Cigarette smoking — no. of pack-yr	37±18	35±19
Lung function		
FEV_1		
Liters	0.86±0.30	0.79±0.27
% of predicted value	29±7	29±8
FVC		
Liters	2.80±0.83	2.50±0.90
% of predicted value	78±16	77±20
RV		
Liters	4.64±1.31	4.43±0.72
% of predicted value	216±36	220±32
TLC		
Liters	7.85±1.54	7.31±1.20
% of predicted value	130±13	133±10
Ratio of RV to TLC — %	59±9	61±8
Carbon monoxide diffusing capacity		
Milliliters of carbon monoxide/min/mm Hg	10.4±3.2	9.8±2.5
% of predicted value	38.7±9.1	39.0±9.7
Arterial blood gas — mm Hg‡		
Partial pressure of oxygen	69±12	69±9
Partial pressure of carbon dioxide	38±6	38±4
Distance on 6-min walk test — m	372±90	377±84
Quality-of-life scores — no. of points§		
St. George's Respiratory Questionnaire	59.1±13.7	59.3±11.6
Modified Medical Research Council scale	2.7±0.8	2.7±0.6
Clinical COPD Questionnaire	2.9±0.8	2.7±0.6
HRCT findings¶		
Target-lobe volume — ml	1993±742	1716±555
Target-lobe voxels below –950 Hounsfield units — %	47.7±8.2	45.7±7.3
Emphysema distribution — no. (%)		
Homogeneous	18 (53)	18 (53)
Heterogeneous	16 (47)	16 (47)

Table 1. (Continued.)

Characteristic	EBV Group (N=34)	Control Group (N=34)
Medical history — no. (%)		
α_1-Antitrypsin deficiency	4 (12)	3 (9)
Previous pneumothorax	2 (6)	1 (3)
Regular physical activity under professional supervision — no. (%)‖	27 (79)	26 (76)

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the two study groups (P>0.05) except for female sex (P=0.01). EBV denotes endobronchial valve, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, HRCT high-resolution computed tomography, RV residual volume, and TLC total lung capacity.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The partial pressure of oxygen and the partial pressure of carbon dioxide were measured while the patient was breathing ambient air.
§ Scores on the St. George's Respiratory Questionnaire range from 0 to 100, with higher scores indicating worse quality of life. Scores on the Modified Medical Research Council scale range from 0 to 4, with higher scores indicating more severe dyspnea. Scores on the Clinical COPD (chronic obstructive pulmonary disease) Questionnaire range from 0 to 6, with higher scores indicating worse functioning.
¶ Emphysema distribution was assessed as the difference in destruction (percentage of voxels of less than –950 Hounsfield units) between the upper and lower lobes in the lung that underwent endobronchial-valve treatment, with a difference of less than 15% defined as homogeneous and a difference of 15% or more defined as heterogeneous.
‖ Patients with regular supervised physical activity had completed a pulmonary rehabilitation program, were receiving maintenance physiotherapy twice a week for their chronic obstructive pulmonary disease, or both. No changes were made in supervised physical activity before or after randomization.

outcomes, and less than 0.05, for secondary outcomes, were considered to indicate statistical significance. For each outcome, response rates were calculated by counting the number of patients who had a change from baseline that met the criterion for a minimal clinically important difference. Fisher's exact test was performed for calculations of between-group differences in outcomes and adverse events. SPSS Statistics, version 22 (IBM), was used for all analyses. For detailed information about study methods, including the statistical analysis, see the Supplementary Appendix, available with the full text of this article at NEJM.org.

RESULTS

STUDY PATIENTS

The study was conducted between June 2011 and November 2014. Eighty-four patients were screened and underwent baseline bronchoscopy. Of these patients, 16 were excluded because they had collateral ventilation (13 patients) or because the airway anatomy was not suitable for endobronchial-valve placement (3), resulting in a total of 68 patients who underwent randomization (Fig. S1 in the Supplementary Appendix). A total of 9 patients in the EBV group and 1 in the control group were not able to complete 6 months of follow-up. Among the patients in the control group who crossed over to endobronchial-valve treatment at 6 months, lobar occlusion was not possible in 3 patients because the airway anatomy was not suitable for endobronchial-valve placement, and this had not been detected during baseline bronchoscopy. Baseline characteristics were similar in the two study groups except that there were more women in the control group than in the EBV group (28 vs. 18, P=0.01) (Table 1).

PROCEDURE

Endobronchial-valve treatment was performed in 34 patients in the first component of the study. A median of four endobronchial valves (range, two to seven) were placed per patient, with a median procedure time of 18 minutes (range, 6 to 51). The median post-treatment hospital stay was 1 day (range, 1 to 13). For a detailed description of the procedure, see Section 9 in the Supplementary Appendix.

PRIMARY OUTCOMES

In the intention-to-treat population, changes from baseline to 6 months in FEV_1, FVC, and 6-minute

walk distance were significantly greater in the EBV group than in the control group (P<0.01 for all comparisons) (Table 2 and Fig. 1).

SECONDARY OUTCOMES

Analyses of data for patients who completed the study (25 patients in the EBV group and 33 in the control group) showed significant improvements in the secondary outcome measures from baseline to 6 months in the EBV group as compared with the control group: the increase in FEV_1 was greater in the EBV group than in the control group by 191 ml (95% CI, 109 to 272), the increase in FVC was greater by 442 ml (95% CI, 215 to 668), and the increase in the 6-minute walk distance was greater by 106 m (95% CI, 80 to 133) (P<0.001 for all between-group comparisons); improvements were also seen in SGRQ scores, with a 14.7-point greater reduction in the EBV group than in the control group (95% CI, –21.8 to –7.6; P<0.001), and in CCQ scores, with a 0.74-point greater reduction in the EBV group than in the control group (95% CI, –1.20 to –0.27; P=0.002). In the EBV group, the median change from baseline in target lobar volume on HRCT was a reduction of 1366 ml (range, –3604 to –28; P<0.001) (Fig. 1, and Table S4 in the Supplementary Appendix). Significantly more patients in the EBV group than in the control group had changes from baseline measures that exceeded the established minimal clinically important difference (P<0.001 for all comparisons) (Table S6 in Supplementary Appendix).

Among patients who completed the study, those who crossed over to endobronchial-valve treatment at 6 months had improvements that were very similar to the improvements in the EBV group (Table S5 in the Supplementary Appendix). Post hoc analysis of HRCT findings in patients who completed the study showed that for patients with heterogeneous emphysema and for those with homogeneous emphysema, there was a significant between-group difference in FEV_1, 6-minute walk distance, residual volume, and SGRQ score in favor of the EBV group at 6 months of follow-up. The effects tended to be larger in patients with heterogeneous emphysema than in those with homogeneous emphysema (Table S7 in the Supplementary Appendix).

ADVERSE EVENTS

One pneumothorax was detected in 84 assessments that were performed by means of the Chartis system. In 7 of the 34 patients in the EBV group (21%), the endobronchial valves were associated with unacceptable adverse events and had to be removed. There were 23 serious adverse events in the EBV group, as compared with 5 in the control group (P<0.001) (Table 3). In the EBV group, treatment-related serious adverse events included pneumothorax (in 18% of patients), other events requiring valve replacement (in 12% of patients) or valve removal (in 15% of patients), and 1 death due to end-stage COPD with respiratory failure 58 days after treatment. All adverse events are listed in Tables S9 and S10 in the Supplementary Appendix.

Pneumothorax

In the EBV group, the frequency of pneumothorax was 18% (6 of 34 patients). In 1 patient, the pneumothorax resolved spontaneously; in 5 patients, insertion of a chest tube was required, with temporary removal of endobronchial valves in 1 patient to promote pneumothorax healing and permanent removal of all valves in 2 patients because of recurrent pneumothorax, after which resolution occurred. No surgical procedures were used to control the pneumothorax.

Repeat Bronchoscopy

Bronchoscopy was repeated in 12 of 34 patients in the EBV group (35%). Reasons for repeat bronchoscopy were permanent removal of endobronchial valves because of recurrent pneumothorax (in 2 patients), torsion of the left-lower-lobe bronchus after left-upper-lobe treatment (in 2), pneumonia distal to the valves (in 1), and markedly increased dyspnea and sputum production without a treatment benefit, as perceived by the patient (in 2); and temporary removal of endobronchial valves to promote healing of a pneumothorax, with valve replacement after 2 months (in 1). Other reasons for repeat bronchoscopy were valve replacement due to migration (in 2), valve dislocation because of granulation-tissue formation (in 1), and persistent cough, with valve replacement in the other lobe (in 1). (For additional information, see Table S9 in the Supplementary Appendix.)

DISCUSSION

We found that endobronchial-valve treatment in patients with emphysema and a proven absence of interlobar collateral ventilation provided a

Table 2. Mean Change from Baseline to 6 Months of Follow-up in Primary Efficacy Outcomes in the Intention-to-Treat Population.*

Variable	EBV Group (N=34)	Control Group (N=34)	Between-Group Difference	P Value
Change in FEV_1				
Milliliters (95% CI)	161 (80 to 242)	21 (–9 to 52)	140 (55 to 225)	0.002
Percentage (95% CI)	20.9 (11.1 to 30.7)	3.1 (–0.4 to 6.6)	17.8 (7.6 to 28.0)	0.001
Response rate — %	59	24	—	0.003
Change in FVC				
Milliliters (95% CI)	416 (201 to 631)	69 (–50 to 187)	347 (107 to 588)	0.005
Percentage (95% CI)	18.3 (9.3 to 27.3)	4.0 (–0.7 to 8.6)	14.4 (4.4 to 24.3)	0.005
Change in distance on 6-min walk test				
Meters (95% CI)	60 (35 to 85)	–14 (–25 to –3)	74 (47 to 100)	<0.001
Percentage (95% CI)	19.6 (10.4 to 28.9)	–3.6 (–6.9 to –0.4)	23.3 (13.6 to 32.9)	<0.001
Response rate — %	59	6	—	<0.001

* Paired t-tests were used to calculate within-group mean differences in changes from baseline to 6 months, P values, and 95% confidence intervals. Two-sample t-tests or, in the absence of a normal distribution, Wilcoxon signed-rank tests were used to calculate between-group mean differences, P values, and 95% confidence intervals. Fisher's exact test was used to calculate the between-group difference in response rates. Response rates were calculated by counting the number of patients for whom the change at 6 months met or exceeded the minimal clinically important difference for FEV_1 (>10%)[10] and the 6-minute walk test (>26 m).[11]

measurable clinical benefit, with significantly improved lung function, exercise capacity, and quality of life, as compared with usual care. The reduction in lung volume with subsequent positive outcomes was accompanied by adverse effects, mainly pneumothorax, which was managed by means of regular care (including chest-tube drainage) but sometimes required repeated bronchoscopy. The endobronchial valves were retained throughout the 6-month study period in 79% of the initially treated patients.

This prospective, randomized, controlled trial confirmed the results of open-label and post hoc studies assessing responses to endobronchial-valve treatment.[1,2,4,18] In the VENT,[1] the overall benefits were moderate, but post hoc analysis showed a significantly greater improvement in FEV_1 in patients with a complete fissure, which indicates an absence of collateral ventilation, than in those with an incomplete fissure. A previous multicenter study validating the Chartis system, which measures collateral ventilation, showed that treatment success was not associated with the method of fissure assessment (i.e., fissure assessment by means of highly dedicated HRCT vs. assessment by means of the Chartis system).[4] However, the current results show that when collateral ventilation is assessed, the overall outcome of treatment is positive. In our study, 84 patients were preselected on the basis of having complete or nearly complete fissures on HRCT scans, with an additional 13 of those patients (15%) excluded on the basis of assessment by means of the Chartis system. We think it is reasonable to speculate that these patients with collateral ventilation would not have had a benefit from endobronchial-valve treatment.

Among the patients who completed the study, there was a significant benefit of the treatment on FEV_1, residual volume, 6-minute walk distance, and scores on the CCQ and SGRQ, with effect sizes all well above the established minimal clinically important differences for these variables (Fig. 1). The improvements with endobronchial-valve treatment tended to be larger in patients with emphysema that was heterogeneous than in those with emphysema that was homogeneous, although we observed improvements in both subgroups, a finding that was also suggested by post hoc analysis of the data from the international VENT.[2] Although comparisons among studies is difficult, it is interesting to note that the improvements we found were of greater magnitude than those noted with pharmacologic treatment in comparable patients and were similar to improvements with surgical lung-volume reduction, but with significantly less morbidity.[19,20]

Even though the trial was randomized and controlled, the large improvements in SGRQ

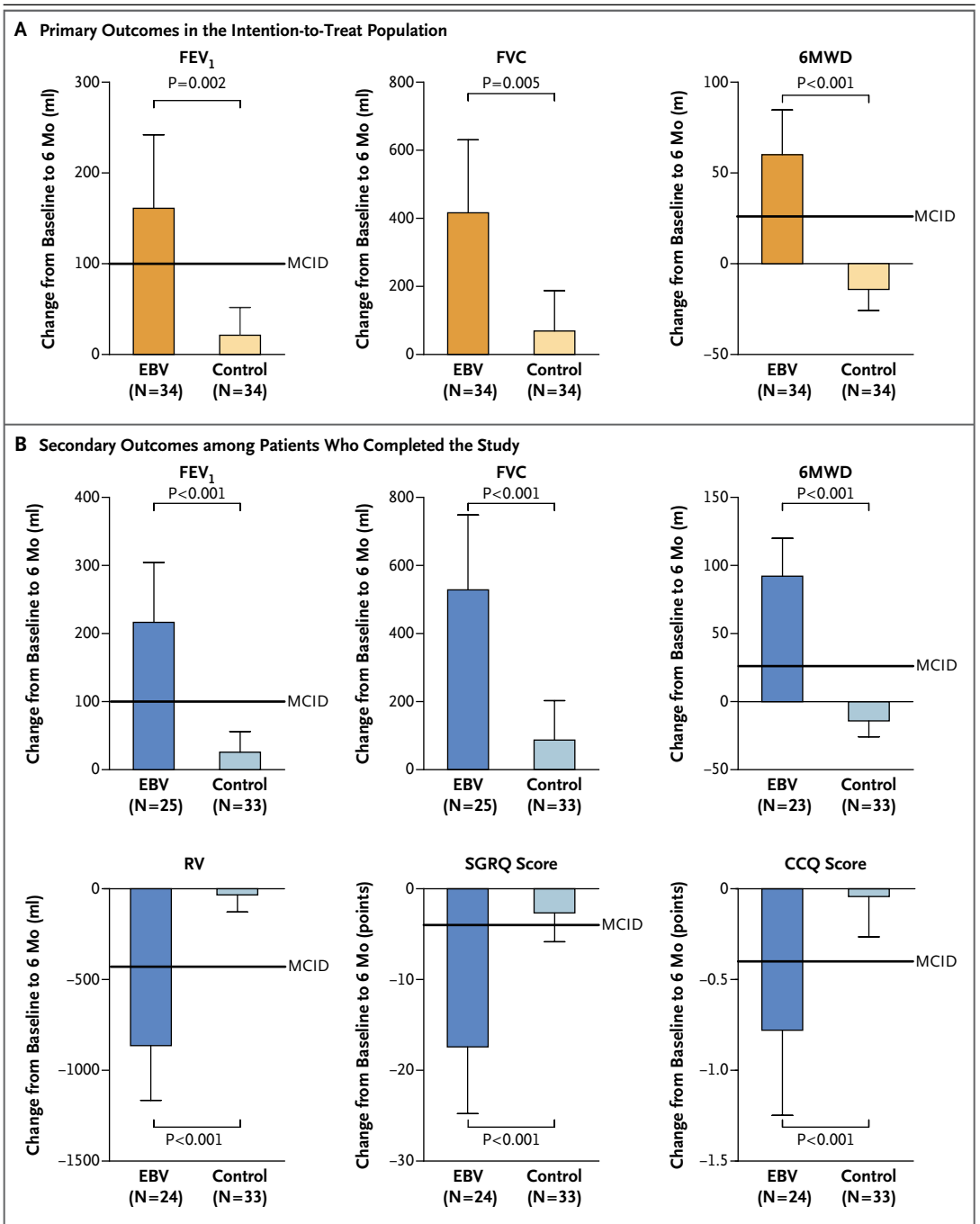

Figure 1. Primary and Secondary Efficacy Outcomes in the Study Groups.

Shown are primary outcomes in the intention-to-treat population (Panel A) and secondary outcomes among patients who completed the study (Panel B), according to the assigned study group (endobronchial-valve [EBV] group or control group). Scores on the St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with higher scores indicating worse quality of life. Scores on the Clinical COPD (chronic obstructive pulmonary disease) Questionnaire (CCQ) range from 0 to 6, with higher scores indicating worse functioning. Horizontal lines represent the minimal clinically important difference (MCID) for the following outcomes: forced expiratory volume in 1 second (FEV_1),[10] an increase of 100 ml; 6-minute walk distance (6MWD),[11] an increase of 26 m; SGRQ score,[8] a reduction of 4 points, CCQ score,[9] a reduction of 0.4 points; and residual volume (RV),[12] a reduction of 430 ml. T bars indicate 95% confidence intervals, and FVC denotes forced vital capacity.

Table 3. Serious Adverse Events during 6 Months of Follow-up.*

Event	EBV Group (N=34)	Control Group (N=34)	P Value†
	no. (%)		
Total no. of serious events	23	5	<0.001
Pulmonary events			
Death	1 (3)‡	0	1.00
COPD exacerbation with hospitalization	4 (12)	2 (6)	0.67
Pneumonia	2 (6)	1 (3)	1.00
Pneumothorax	6 (18)	0	0.02
Resolved ≤14 days after onset, without drainage	1 (3)	0	1.00
Resolved ≤14 days after onset, with drainage	2 (6)	0	0.49
Required temporary valve removal	1 (3)§	NA	NA
Required permanent valve removal because of recurrent pneumothorax	1 (3)	NA	NA
Required permanent valve removal, after temporary removal and reimplantation, because of recurrent pneumothorax	1 (3)	NA	NA
Other EBV-related events requiring permanent removal of all valves			
Torsion of the bronchus	2 (6)¶	NA	NA
Pneumonia distal to valve	1 (3)‖	NA	NA
Increased sputum, dyspnea, or coughing without patient-perceived treatment benefit	2 (6)	NA	NA
Other EBV-related events requiring valve replacement			
Valve migration	2 (6)	NA	NA
Valve expectoration	0	NA	NA
Valve dislocation due to formation of granulation tissue	1 (3)	NA	NA
Increased sputum, dyspnea, or coughing	1 (3)	NA	NA
Stroke	1 (3)	2 (6)	1.00

* Serious adverse events were all adverse events that were fatal, required or prolonged hospitalization, caused substantial risk of death at the time of the event, resulted in permanent impairment of a body function, or required medical or surgical intervention to prevent permanent impairment of a body function. Nonserious adverse events during 6 months of follow-up are listed in Table S10 in the Supplementary Appendix. NA denotes not applicable.

† A two-sided Fisher's exact test was used to calculate the difference in adverse events between the EBV group and the control group.

‡ The patient died from end-stage chronic obstructive pulmonary disease with respiratory failure 58 days after endobronchial-valve treatment.

§ The valve was removed temporarily to expand the target lobe; the pneumothorax resolved, and at 49 days, the valve was reimplanted.

¶ Both patients had low oxygen saturation and dyspnea after endobronchial-valve treatment in the left upper lobe; CT scans confirmed torsion of the left lower bronchus. In both cases, the valves were removed at 14 days, with complete recovery after removal.

‖ Postobstruction pneumonia developed in the treated lobe 163 days after treatment; valves were removed, and the patient recovered.

scores could have been influenced by the open-label design. A previous trial of bronchoscopic intervention, in which a sham control was used, showed that placebo effects were limited in patients with severe COPD.[21] Two other sources of potential bias should be considered: both patients and bronchoscopists were aware of the treatment assignment at the time of bronchoscopy, and the revealed treatment assignments for the patients with collateral ventilation or unsuitable airways for endobronchial-valve placement were put back in the randomization sequence in newly

sealed envelopes. However, baseline characteristics were similar in the two study groups, except for sex distribution. In addition, the results for the patients in the control group who crossed over to endobronchial-valve treatment at 6 months were similar to those for the original EBV group.

Pneumothorax, which was the most frequent adverse event, is thought to be due to a rapid shift in lung volumes caused by the rupture of blebs or bullae, the rupture of parenchyma due to pleural adhesions, or the response to barotrauma.[22] The observed frequency of pneumothorax (18%) in our study was higher than the frequencies reported in earlier trials (VENT in 2010, 4%[1]; Chartis trial in 2013, 8%[4]) but was similar to the frequency in an analysis of German data from 2014 (23%[23]). This increase in the frequency of pneumothorax is probably the result of more successful execution of endobronchial-valve treatment (resulting in a higher percentage of patients having a significant reduction in lobar volume) and patient selection (i.e., patients without collateral flow). All cases of pneumothorax in the EBV group occurred within 1 day after endobronchial-valve treatment, when the patients were still hospitalized. Because a pneumothorax is a potentially life-threatening complication in patients with severe emphysema, we found that close monitoring of patients after endobronchial-valve treatment, including monitoring after discharge, was crucial. All cases of pneumothorax in our study were managed according to published guidelines.[22,24]

Repeat bronchoscopy is sometimes necessary to replace or temporarily or permanently remove endobronchial valves. Reasons to do so include loss of initial lung-volume reduction due to formation of granulation tissue or valve migration. Previous studies postulated that endobronchial-valve treatment is fully reversible and does not preclude future therapeutic options.[1,2,4] Our study provides confirmation of this view, since all patients in whom endobronchial valves were removed recovered without further side effects.

In conclusion, we found that in patients with severe emphysema who were preselected on the basis of a proven absence of interlobar collateral ventilation, endobronchial-valve treatment improved pulmonary function, exercise capacity, and quality of life, even when we considered patients in whom valve removal was required. Adverse events, including potentially life-threatening events, occurred and required careful follow-up.

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